Association Between Sodium Intake and Change in Uric Acid, Urine Albumin Excretion, and the Risk of Developing Hypertension

John P. Forman, MD, MSc; Lieneke Scheven, MD; Paul E. de Jong, MD, PhD; Stephan J.L. Bakker, MD, PhD; Gary C. Curhan, MD, ScDr; Ron T. Gansevoort, MD, PhD*

Background—A high-sodium diet has little short-term effect on blood pressure in nonhypertensive individuals but, for unclear reasons, is associated with hypertension if consumed long term. We hypothesized that a chronically high sodium intake would be associated with increases in biomarkers of endothelial dysfunction, specifically serum uric acid (SUA) and urine albumin excretion (UAE), and that high sodium intake would be associated with incident hypertension among those with higher SUA and UAE.

Methods and Results—We prospectively analyzed the associations between sodium intake and the change in SUA (n=4062) and UAE (n=4146) among participants of the Prevention of Renal and Vascular End Stage Disease (PREVEND) study who were not taking antihypertensive medications. We also examined the association of sodium intake with the incidence of hypertension (n=5556) among nonhypertensive participants. After adjustment for confounders, each 1-g-higher sodium intake was associated with a 1.2-mol/L increase in SUA (P=0.01) and a 4.6-mg/d increase in UAE (P<0.001). The relation between sodium intake and incident hypertension varied according to SUA and UAE. For each 1-g-higher sodium intake, the adjusted hazard ratio for developing hypertension was 0.98 (95% confidence interval, 0.89–1.08) among those in the lowest tertile of SUA and 1.09 (1.02–1.16) among those in the highest tertile. Corresponding hazard ratios were 0.99 (confidence interval, 0.93–1.06) among participants whose UAE was <10 mg/d and 1.18 (confidence interval, 1.07–1.29) among those whose UAE was >15 mg/d.

Conclusions—Over time, higher sodium intake is associated with increases in SUA and UAE. Among individuals with higher SUA and urine UAE, a higher sodium intake is an independent risk factor for developing hypertension. (Circulation. 2012;125:3108-3116.)

Key Words: diet ■ epidemiology ■ hypertension ■ risk factors ■ sodium

Most individuals consume sodium far in excess of the recommendations from major health organizations.¹ A high-salt diet is believed to be responsible for 20% to 40% of all cases of hypertension in the United States² and 6% of myocardial infarctions and strokes annually.³

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Evidence in nonhypertensive humans and experimental animals indicates that a long-term high sodium intake is associated with increases in blood pressure over time.²,³,⁴,⁵,⁶,⁷,⁸ Paradoxically, short-term sodium loading in these healthy humans and animals does not substantially increase blood pressure.⁹,¹⁰ How individuals who are not initially salt sensitive can develop hypertension related to chronic sodium loading is not well understood. However, studies in humans and animals have shown that short-term sodium loading is associated with endothelial dysfunction and vascular injury.⁴,¹¹–¹⁶ and it is possible that such insults, if repeated over the long term, could explain the increasing blood pressure associated with a chronically high-salt diet. A high-salt diet may also induce salt sensitivity, as has been reported in rodents, possibly through endothelial dysfunction.⁴

Higher serum uric acid (SUA) and a higher urinary albumin excretion (UAE) are well-established markers of endothelial dysfunction,¹⁷–²⁵ and both are independently associated with an increased risk of hypertension.²⁶–³⁰ We hypothesized that a higher sodium intake would be positively associated with a longitudinal increase in SUA and UAE and that higher SUA and UAE would modify the association between sodium intake and hypertension. We investigated
these hypotheses in participants of the Prevention of Renal and Vascular End Stage Disease (PREVEND) study.

Methods

Study Population

The PREVEND study is a large, ongoing, prospective cohort initiated in 1997 when 40,856 people from the general population of Groningen, the Netherlands, were screened. Recruitment was based on the screening urine albumin concentration to enrich the cohort with individuals with albuminuria. A total of 8592 participants completed the first examination between 1997 and 1998.31,32 Of these, 6894 participants completed a second examination between 2001 and 2003, and 5862 completed a third examination between 2003 and 2006.33

To perform the analyses of sodium intake and risk of hypertension, we limited our study population to 5556 participants who did not have prevalent hypertension (defined below) at the time of their initial examination and had available measurements of urine sodium (Figure 1). To examine the associations of sodium intake with changes in SUA and UAE between the baseline (first) and third examinations, we excluded individuals who were taking antihypertensive medications at the first or third examinations because antihypertensive interventions can affect the levels of SUA and UAE; we also excluded those with missing data on SUA or UAE. After exclusions, 4062 participants were included in the analysis of change in SUA, and 4146 participants were included in the analysis of change in UAE.

The PREVEND study has been approved by the medical ethics committee at the University Medical Center Groningen, and the present analysis was approved by the institutional review board at Brigham and Women’s Hospital. All participants gave written informed consent.

Assessment of Sodium Intake

Throughout this article, we refer to sodium rather than salt because major societies that issue guidelines such as the Joint National Committee34 and European Society of Hypertension35 make recommendations for restriction of “sodium.” Each 43 mmol of sodium is approximately equivalent to 1 g of sodium or 2.5 g of salt (sodium chloride).

Sodium intake was assessed by urinary sodium excretion. Participants collected two 24-hour urine specimens at each of the 3 examinations. Determination of urine sodium concentration was performed on specimens from the first and second examinations by indirect potentiometry with a MEGA clinical chemistry analyzer (Merck, Darmstadt, Germany); the sodium concentration was multiplied by the urine volume to obtain a value in milligrams per 24 hours. For each examination, we used the mean value of the two 24-hour collections. The correlation coefficients among participants’ sodium intake across the longitudinal examinations were 0.55 (in the whole cohort) and 0.66 (in just those who did not develop hypertension).

Assessment of SUA and UAE

Serum concentrations of uric acid were measured with a MEGA clinical chemistry analyzer with the uricase PAP (Preatorius and Poulson) method and expressed as micromoles per liter (divide by 59.48 to obtain the SUA in mg/dL). Urine albumin concentration was measured on 24-hour urine specimens by nephelometry (Dade Behring Diagnostic, Marburg, Germany); the threshold value was 2.3 mg/L and intra-assay and interassay coefficients of variation were <2.2% and 2.6%, respectively. The urine albumin concentration was multiplied by the total urine volume to obtain a UAE in milligrams per 24 hours; the UAE at each examination was defined as the mean value of the 2 collections. We defined the change in SUA and UAE as the mean values for SUA and UAE at the first (baseline) examination.

Assessment of Hypertension

At each examination, blood pressure was measured on the right arm with an automated device (Dinamap XL model 9300; Johnson & Johnson Medical, Tampa, FL) for 8 to 10 minutes...
while the participant was supine. The blood pressure for the visit was defined as the mean of the last 2 readings. Use of antihypertensive medications was ascertained by questionnaire at each visit and was complemented by information garnered from community pharmacies.

Hypertension was defined as a systolic pressure ≥140 mm Hg, a diastolic pressure ≥90 mm Hg, or both or the use of antihypertensive medications in concordance with recommendations from the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Participants who already had hypertension at the baseline examination were excluded; incident hypertension was defined as hypertension that occurred after the baseline examination.

Assessment of Covariates
The procedures at each examination in the PREVEND study have been described in detail previously. Briefly, each of the 3 examinations included 2 visits to the outpatient unit separated by 3 weeks. Participants completed questionnaires that gathered demographic information and detailed information about health-related behaviors (such as smoking and alcohol use), diagnoses of cardiovascular and renal disease, medication use, and family history. In addition to blood pressure measurements, participants had assessments of height and weight and provided fasting blood samples and 24-hour urine specimens.

Body mass index was calculated as weight in kilograms divided by height in meters squared. Urine potassium was determined by indirect potentiometry with a MEGA clinical chemistry analyzer. With the same analyzer, urine calcium was determined by a photometric test with an o-Cresolphthalein complex, and urine uric acid was measured with the uricase PAP method. Concentrations of serum and urine creatinine, serum glucose, and serum total cholesterol were determined by enzymatic methods with a Kodak Ektachem dry chemistry autoanalyzer (Eastman Kodak, Rochester, NY). Estimated glomerular filtration rate was calculated from the Chronic Kidney Disease Epidemiology Collaboration equation. Smoking status was categorized as never smoked, quit <1 year earlier, quit >1 year previously, and actively smoking. Alcohol intake was categorized as none, 1 to 4 beverages per month, 2 to 7 beverages per week, 1 to 3 beverages per day, and ≥4 beverages per day.

Statistical Analyses
Sex-adjusted associations between sodium intake and other covariates at baseline were analyzed with linear regression. The associations were displayed visually as medians and interquartile ranges for each covariate stratified by quartile of sodium intake. Urinary sodium excretion as a marker for sodium intake was analyzed as a continuous variable (per 1-g-higher intake) and in quartiles. The associations of sodium intake with the longitudinal changes in SUA and UAE were examined among the subset of participants with available data who were also not using antihypertensive medication at the final visit. These analyses used linear regression, with sodium intake as the independent variable and changes in SUA and UAE as the dependent variables. Multivariable models adjusted for age, body mass index, sex, alcohol intake, smoking status, systolic and diastolic blood pressures, estimated glomerular filtration rate, plasma levels of glucose and cholesterol, and urinary levels of potassium, calcium, and creatinine. In addition, models were mutually adjusted for baseline levels of SUA and urinary albumin.

The association between sodium intake and risk for incident hypertension was analyzed with multivariable Cox proportional hazards regression; stratified models by tertile of SUA or clinical category of UAE (<10 mg/d [n=3490], 10–15 mg/d [n=1051], and >15 mg/d [n=1015]) were constructed to examine whether the association between sodium intake and hypertension risk varied according to SUA and UAE. In these proportional hazards regression models, person-time was counted from the date of the first examination until the date that hypertension was diagnosed, the date of death, or the date of the last examination, whichever came first. Multivariable models were adjusted for age, body mass index, sex, alcohol intake, smoking status, family history of hypertension, estimated glomerular filtration rate, plasma levels of glucose and cholesterol, and urinary levels of potassium, calcium, and creatinine. Multiplicative interaction terms were created between sodium intake and SUA and between sodium intake and UAE. Effect modification of the associations between sodium intake and hypertension risk by SUA and UAE was then tested by including these interaction terms in unstratified multivariable models that also included terms for the main effects of sodium intake and either SUA or UAE. The proportional hazards assumption was tested by analyzing the interaction between sodium intake and calendar-time; there was no significant interaction between sodium intake and calendar-time. Finally, we examined the possibility of a nonlinear relation between sodium intake and incident hypertension nonparametrically with restricted cubic splines. Tests for nonlinearity used the likelihood ratio test, comparing models with only the linear term and models with both linear and cubic spline terms. SAS version 9.1 (SAS Institute, Cary, NC) was used for all analyses, and all P values were 2 sided.

Results
A total of 5556 participants who did not already have hypertension at the time of the first examination and had available measurements of urine sodium were included in the analysis of incident hypertension (Figure 1). The baseline characteristics of this study population, according to quartile of sodium intake, are displayed in Table 1. At baseline, a higher sodium intake was associated with higher SUA and UAE, as well as higher systolic and diastolic pressures, higher body mass index, higher serum glucose, and a higher prevalence of active smoking and alcohol use. Women consumed less sodium than men. Age, estimated glomerular filtration rate, plasma total cholesterol, and family history of hypertension were not associated with sodium intake at baseline. The baseline characteristics of the 4062 participants who were analyzed for change in SUA and the 4146 participants who were analyzed for change in UAE were not different from the baseline characteristics of the 5556 participants analyzed for incident hypertension.

We analyzed the association between sodium intake and change in SUA among the 4062 participants with available SUA levels at both the first (baseline) examination and third examination who did not take antihypertensive medication (Table 2). The median SUA of the entire population increased from the first to the third examination by 17.8 μmol/L, and this increase was larger among those who consumed more sodium. For every 43-mmol (=1 g)-higher sodium intake, the adjusted change in SUA was 1.4 μmol/L larger (95% confidence interval [CI], 0.2–2.6; P=0.01). Compared with those in the lowest quartile of sodium intake (<123 mmol/d), those in the highest quartile (>221 mmol/d) had a 6.0-μmol/L (95% CI, 1.3–10.7) -larger adjusted change in SUA (Table 2 and Figure 2A).

We also analyzed the association between sodium intake and change in UAE among 4146 individuals who had UAE measured at both the first and third examinations and were not treated with antihypertensive medications (Table 2). The median UAE increased for the whole population by 0.4 mg/d during the period of follow-up. The change in UAE was larger among participants who consumed greater amounts of sodium. The adjusted change in UAE was 4.6 mg/d larger for.
During a median follow-up of 6.4 years, 878 incident cases of hypertension accrued. Sodium intake was significantly associated with incident hypertension. The crude hypertension incidence for the entire population without hypertension at baseline was 15.8%. The incidence was 19.7% among those in the lowest quartile (Table 2 and Figure 2B).

After adjustment for age, the hazard ratio for incident hypertension per 1-g-higher sodium intake was 1.06 (95% CI, 1.02–1.11). Compared with the lowest quartile of sodium intake, the age-adjusted hazard ratio for incident hypertension among those in the highest quartile of sodium intake was 1.29 (95% CI, 1.05–1.60). After additionally controlling for body mass index, sex, alcohol intake, smoking status, family history of hypertension, estimated glomerular filtration rate, serum levels of glucose and cholesterol, and urinary levels of potassium, calcium, and creatinine, the hazard ratio was 1.05 (95% CI, 1.00–1.10) for each 1-g-higher sodium intake and 1.21 (95% CI, 0.98–1.51) comparing the highest with lowest quartile of sodium intake. The association of sodium intake with incident hypertension was modified by both SUA and UAE (Table 3 and Figure 3). A 1-g-higher sodium intake was associated with an adjusted hazard ratio of 0.98 (95% CI, 0.89–1.08) among each additional 1 g of sodium consumed (95% CI, 2.2–7.0; P<0.001). Those in the highest quartile of sodium intake had a 6.5-mg/d (95% CI, −2.6 to 15.6) larger change in UAE compared with those in the lowest quartile (Table 2 and Figure 2B).

Table 2. Association Between Sodium Intake and Longitudinal Changes in Serum Uric Acid and Urine Albumin Excretion

| Characteristic | 97 (79–110); n = 1389 | 142 (132–153); n = 1389 | 188 (176–203); n = 1389 | 271 (242–316); n = 1389 | sex-
| Adjusted P |
|----------------|-----------------|-----------------|-----------------|-----------------|------|
| Urac acid, μmol/L | 261.7 (220.1–321.2) | 279.6 (237.9–273.1) | 279.6 (237.9–273.1) | 297.4 (249.8–350.9) | 0.02 |
| Urine albumin excretion, mg/d | 7.3 (5.3–11.7) | 7.9 (5.8–12.5) | 8.4 (6.1–13.6) | 8.7 (6.4–13.9) | 0.002 |
| Age, y | 43 (36–52) | 43 (36–52) | 43 (36–52) | 44 (37–52) | 0.08 |
| BMI, kg/m² | 23.7 (21.7–26.2) | 24.2 (22.2–26.7) | 24.9 (22.6–27.3) | 25.7 (23.5–28.4) | <0.001 |
| Systolic blood pressure, mm Hg | 116 (108–126) | 118 (110–127) | 119 (111–128) | 121 (112–129) | <0.001 |
| Diastolic blood pressure, mm Hg | 69 (64–74) | 70 (65–75) | 70 (65–75) | 71 (65–76) | 0.01 |
| Estimated GFR, mL·min⁻¹·1.73 m⁻² | 87 (77–97) | 87 (77–96) | 87 (77–97) | 87 (78–98) | 0.84 |
| Serum glucose, mmol/L | 5.3 (4.2–4.9) | 4.6 (4.2–4.9) | 4.6 (4.2–4.9) | 4.7 (4.2–4.9) | <0.001 |
| Total cholesterol, mmol/L | 114 (78–158) | 140 (97–188) | 163 (115–210) | 182 (131–243) | <0.001 |
| Urine calcium, mg/d | 5 (3.9–7.7) | 5.4 (4.7–6.2) | 5.4 (4.7–6.2) | 5.4 (4.8–6.2) | 0.18 |
| Urine creatinine, g/d | 229 (151–286) | 273 (198–344) | 308 (220–378) | 358 (270–436) | <0.001 |
| BMI indicates body mass index; GFR, glomerular filtration rate. Estimated GFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation. P values were determined by linear regression with urine sodium as the dependent variable and were adjusted for sex.
those in the lowest tertile of SUA (<255.8 μmol/L) and with an adjusted hazard ratio of 1.09 (95% CI, 1.02–1.16) among those in the highest tertile of SUA (>309.3 μmol/L); the $P$ value for the interaction between sodium intake and SUA was <0.001. When we stratified by category of UAE, the hazard ratio of developing hypertension for each 1-g-higher sodium intake was 0.99 (95% CI, 0.93–1.06) among participants whose UAE was <10 mg/d and 1.18 (95% CI, 1.07–1.29) among those whose UAE was >15 mg/d; the $P$ value for the interaction between sodium intake and UAE was 0.007. Further controlling for baseline systolic and diastolic blood pressures did not materially alter these results. The association of sodium intake with incident hypertension was close to linear in our nonparametric analysis ($P$ for linearity=0.06) and was linear among those participants in the highest tertile of SUA ($P$ for linearity=0.05) and the highest category of UAE ($P$ for linearity=0.02).

**Discussion**

In this prospective, population-based cohort, we found that a higher sodium intake was independently associated with larger increases in markers of vascular endothelial dysfunction over time, specifically SUA and UAE. In addition, the association between sodium intake and incident hypertension was modified by these markers of vascular endothelial dysfunction, and sodium intake was an independent risk factor only among those with higher levels of SUA and UAE. Thus, a high-sodium diet may lead to biological changes favoring the development of hypertension if the high-sodium diet is continued.

More than 30 years ago, Guyton et al9 drew attention to the contradiction between the short-term and long-term effects of sodium loading on blood pressure. In the short term, a high-sodium diet has minimal effect on the blood pressure of normal individuals and experimental animals.37–39 However, sodium loading led to substantial increases in the blood pressure of those who had a reduction in kidney mass, infusion of angiotensin II, or endothelial dysfunction (ie, individuals who are salt sensitive).37,38,40–42 In contrast to short-term sodium loading, long-term sodium loading is associated with the development of hypertension in initially normal populations. This has been demonstrated in various natural experiments, notably in Cook Islanders4; specifically, lifetime blood pressure remained low among the residents of one island where access to sodium-rich food was limited, whereas blood pressure increased with age among a population of genetically similar inhabitants of a nearby island with ample access to sodium-rich food.4 Identical observations have been made in rodents who, after weaning, were randomly assigned to consume high-sodium or low-sodium chow.7 Thus, a high-sodium diet may have minimal short-term effects on blood pressure but, if continued over long

Table 3. Association Between Sodium Intake and Hazard Ratio of Hypertension According to Level of Uric Acid or Albumin Excretion

<table>
<thead>
<tr>
<th>Model</th>
<th>Continuous Urine Sodium (per Each 43-mmol Increase)</th>
<th>Quartile of Urine Sodium, Median (Interquartile Range), mmol/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>97 (79–110)</td>
</tr>
<tr>
<td>Multivariable HR (95% CI) according to category of uric acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tertile 1 (&lt;255.8 μmol/L)</td>
<td>0.98 (0.89–1.08)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Tertile 2 (255.8–309.3 μmol/L)</td>
<td>1.05 (0.96–1.15)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Tertile 3 (&gt;309.3 μmol/L)</td>
<td>1.09 (1.02–1.16)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>Multivariable HR (95% CI) according to category of albumin excretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 mg/d</td>
<td>0.99 (0.93–1.06)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>10–15 mg/d</td>
<td>1.02 (0.92–1.12)</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td>&gt;15 mg/d</td>
<td>1.18 (1.07–1.29)</td>
<td>1.0 (Reference)</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval. For sodium, 43 mmol is ≈1 g of sodium. Multivariable models were adjusted for age, body mass index, sex, alcohol intake, smoking status, family history of hypertension, estimated glomerular filtration rate, plasma levels of glucose and cholesterol, and urinary levels of potassium, calcium, and creatinine. $P<0.001$ for the interaction between sodium intake and serum uric acid; $P=0.007$ for the interaction between sodium intake and urinary albumin excretion.
periods of time, may ultimately result in progressive increases in blood pressure.

The mechanisms that underlie the association between chronic sodium loading and hypertension are incompletely understood. Rodent data suggest that sodium loading leads to suppression of nitric oxide synthase in vascular beds, generating endothelial dysfunction.4,13,15 In humans, sodium loading also seems to produce endothelial dysfunction.11,14,16 As an example, the effect of a high-sodium diet on brachial endothelium-dependent vasodilation was determined in 16 healthy, nonhypertensive individuals in a randomized double-blind crossover trial. Compared with a low-sodium diet (76 mmol/d), endothelium-dependent vasodilation was 36% reduced (P < 0.05) when daily sodium intake was supplemented (mean total intake of 225 mmol/d).16 In addition to endothelial dysfunction, a high-sodium diet may lead to anatomic capillary rarefaction.12 Capillary rarefaction, or a decrease in the number of capillaries, is a well-established abnormality in people with hypertension43 and may predate the onset of hypertension.44 Because, as noted earlier, individuals with endothelial dysfunction and vascular damage are more likely to be sodium sensitive, it is possible that long-term high sodium intake may create a state of sodium sensitivity. Indeed, this phenomenon has been noted in rats that transitioned from sodium resistant to sodium sensitive after 8 weeks on a high-sodium diet.4 Thus, long-term sodium loading may lead to endothelial dysfunction and vascular damage, which in turn may exacerbate the pressor effects of a high-sodium diet in an amplification loop.

Higher SUA and UAE are markers of endothelial dysfunction in humans17–25 and therefore may also be markers of sodium sensitivity.45–50 The association of SUA with endothelial dysfunction was illustrated in 217 individuals with mild untreated hypertension who underwent measurement of endothelium-dependent brachial artery vasodilation.25 Compared with participants whose SUA was ≥3.5 mg/dL, endothelium-dependent vasodilation was 33% worse among those with SUA levels of ≥5.5 mg/dL; other studies have found similar associations.18,19,23 In rats, hyperuricemia induced by the inhibition of the uricase enzyme for just 9 weeks induces persistent sodium sensitivity, even after the SUA is lowered to normal.50 In humans, an association between SUA and sodium sensitivity was documented in a small study of 21 healthy volunteers; the correlation coefficient was 0.31, which was not statistically significant.49 The relation between UAE and endothelial dysfunction is well established.57–22,24 In addition, higher UAE is associated with sodium sensitivity.45–48 In 177 healthy volunteers, for example, the prevalence of sodium sensitivity was significantly higher in those whose UAE was 15 to 20 mg/d compared with those whose UAE was ≤10 mg/d (67% versus 24%).47 Taken together, these data suggest that higher levels of SUA and UAE indicate the presence of endothelial dysfunction and, as a result, may identify those at higher risk for hypertension when sodium intake is high.

We found that a higher sodium intake was associated with greater longitudinal increases in SUA and UAE. To the best of our knowledge, the relation between sodium intake and increasing SUA is novel. However, the effects of sodium intake on albumin excretion have been documented in several clinical trials51–53 and in observational studies.54 In the largest of these trials, 71 whites, 69 blacks, and 29 Asians received sodium supplements for 6 weeks and placebo for 6 weeks, given in random order.51 UAE increased significantly with
sodium supplements from 9.1 to 10.2 mg/d; this increase may have been due to a change in blood pressure, which also increased with sodium supplements. In our study, a 1-g increase in sodium intake was also associated with a modestly increased risk of developing hypertension. This finding is consistent with some, but not all, prospective cohort studies. Among 1520 Taiwanese men and women followed up for an average of 7.9 years, for example, the risk of developing hypertension was 26% higher (95% CI, 1–57) among those whose baseline 24-hour urinary sodium excretion was ≥178 mmol/d compared with those whose sodium intake was estimated to be <123 mmol/d. On the other hand, there was no association between urinary sodium excretion and incident hypertension in 2096 Europeans followed up for a median of 6.5 years. However, the CIs were wide and incorporated the hazard ratio that we observed. Furthermore, the hypertension incidence rates according to category of urinary sodium excretion began to diverge after ∼6 years of follow-up, and the incidence thereafter was higher among those who consumed more sodium. Our finding is also consistent with the combined experience from randomized trials of sodium reduction, which indicate that long-term reductions in sodium lower blood pressure.

We found that the association between sodium intake and risk for developing hypertension depended upon SUA and UAE. In stratified models, sodium intake was independently associated with incident hypertension in participants who were in the highest tertile of SUA or who had UAE >15 mg/d. The dependence of the sodium-hypertension association upon SUA and UAE may reflect differences in sodium sensitivity, which, in and of itself, is a significant and independent predictor of hypertension incidence. Modification of the effect of sodium intake on blood pressure has been described previously in meta-analyses. As an example, a modest reduction in sodium intake lowered systolic blood pressure by 5.2 mm Hg in 28 trials of hypertensive individuals and by 1.3 mm Hg in 19 trials of normotensive individuals (P for interaction <0.001). In addition, the effect of sodium on blood pressure tended to be larger in older compared with younger individuals. To the best of our knowledge, however, no studies have examined whether the association between sodium intake and risk for hypertension is modified by markers of endothelial dysfunction, which could be indicators of a sodium-sensitive state.

Our study has multiple strengths, including the use of a large prospective community-based cohort, the use of multiple 24-hour urine specimens to estimate each participant’s sodium intake and to define their UAE, the use of multiple measured blood pressures and participant and pharmacy information on antihypertensive medication to define hypertension, extensive adjustment for covariates that are associated with hypertension and thus potential confounders, and updating of sodium intake and covariate information midway through the period of follow-up to reduce potential misclassification. Our study also has important limitations. First, ∼30% of those who participated in the first examination did not participate in the third examination, in large part because of refusal or death. However, the baseline characteristics of those who were lost to follow-up and those who completed the third examination were only marginally different (data not shown); therefore, the likelihood for survival bias is low. Moreover, because individuals with hypertension may be more likely to be lost to follow-up owing to cardiovascular disease, any survival bias that was introduced would likely lead to an underestimation of the true association between sodium intake and hypertension. Second, this PREVEND cohort is almost entirely white, which limits the generalizability of our findings. Nevertheless, several of our findings, namely the association between sodium intake and changes in albuminuria and the relation between sodium intake and incident hypertension, have been previously observed in black populations. Third, our definition of hypertension was based in part on measurement of supine blood pressure, whereas consensus recommendations (such as from the Joint National Committee) advocate ascertainment of seated blood pressure. However, except for elderly individuals and those with hypovolemia, supine and seated blood pressures should differ only minimally. Finally, as with any observational study, residual confounding may explain our findings; at least in part. As an example, a higher sodium intake may be a marker for other unhealthy lifestyle choices that we did not measure and therefore could not include in our multivariable models such as physical activity or intake of sugar-sweetened beverages. On the other hand, we adjusted for numerous known risk factors for hypertension, including adiposity, and extensive physiological and experimental studies provide a plausible mechanism linking sodium intake with hypertension.

Conclusions
A higher sodium intake over time is associated with greater increases in 2 markers of endothelial dysfunction, namely SUA and UAE. In addition, a higher sodium intake is associated with an increased risk of developing hypertension, principally in those individuals who have higher levels of SUA and UAE. Taken together, these results suggest that a high-sodium diet over the long term may lead to endothelial dysfunction and vascular damage, generating a biological state in which continuance of the high-sodium diet may produce hypertension (a sodium amplification loop). These findings should be tested in other prospective cohorts and, if possible, in randomized trials.

Sources of Funding
This work was funded by the American Heart Association (2009A050171) and the National Institutes of Diabetes Digestive and Kidney Disease (DK091417). The PREVEND study has been made possible by grants from the Dutch Kidney Foundation. The funders of this work had no role in the conception, execution, or analysis of the research and had no role in drafting of the manuscript. We also thank Dade Behring (Marburg, Germany) for supplying equipment (specifically the Behring Nephelometer II) and reagents for nephelometric measurement of urinary albumin concentration.

Disclosures
None.
References

Although a short-term sodium load does not usually raise blood pressure, a long-term high sodium intake is associated with increases in blood pressure. The reasons for this are unclear. Our study suggests that a high-sodium diet over the long term may lead to endothelial dysfunction and vascular damage, generating a biological state in which continuance of the high-sodium diet may produce hypertension (a sodium amplification loop).
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Circulation. 2012;125:3108-3116; originally published online June 18, 2012; doi: 10.1161/CIRCULATIONAHA.112.096115
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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